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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,032	06/29/2001	Christoph Seidel	HUBR-1067.3 DIV	2111

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EXAMINER	
BROWN, TIMOTHY M	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/896,032	SEIDEL ET AL.	
	Examiner	Art Unit	
	Timothy M. Brown	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Final Office Action is responsive to the communication received December 5, 2005. Claims 40-48 are under examination.

Response to Arguments

In the preceding Office action, the claims were rejected because they lacked enablement for the breadth of cysteine modifications claimed. It was noted that cysteine modifications have a very unpredictable effect on antigenicity. Applicants argue that this is the wrong standard for determining enablement. The Examiner respectfully disagrees.

The level of predictability in the art is just one factor that must be considered under the *Wands* analysis. Applicant claims a method for detecting HCV antibody comprising contacting a sample with an antigenic NS3 peptide that has been modified at one or more cysteine residues. Thus, evaluating the effects of cysteine modifications on the antigenicity of the NS3 peptide is relevant to whether or not the claims are enabled. The preceding Office action cites numerous references that show cysteine modifications have drastic adverse effects on antibody specificity. Therefore, the unpredictability of cysteine modifications strongly suggests that the claimed modifications are not enabled.

Applicants note that their antigen does not have to have any particular degree of affinity for HCV antibody. Applicants therefore reason that modifications that decrease binding would not necessarily prevent their assay from working. This argument is not persuasive since the art shows that the claims embrace cysteine modifications that would completely disrupt HCV antibody binding. Moreover, specificity for HCV antibody requires a certain level of antigen

affinity. Using antigens that only bind antibody weakly would not work since other non-specific interactions would prevent NS3 antibody from binding.

Applicants argue the claims do not require undue experimentation because reducing the invention to practice would only require comparing the binding of modified and unmodified NS3 peptides. This argument however ignores the range of potential modifications. The NS3 polypeptide has around 631 amino acid residues and the claims allow modifying any combination of cysteine residues. The claims allow the NS3 cysteine residues to be modified by deletion, substitution, or insertion. Given that there are 20 natural amino acids that can be substituted or inserted in any possible combination, deriving those cysteine modifications that permit NS3 antibody specificity would take extensive experimentation. Thus, the level of experimentation required is another factor that suggests that the claims are not enabled.

Applicants suggest that the references used to show the unpredictable effects of cysteine modifications are not persuasive for two reasons. First, the references do not qualify as prior art. Second, the references do not relate to HCV or the NS3 regions. Regarding the first point, the references were only offered to show how cysteine modifications produce different effects on antibody specificity. The references show this was a fact of nature that challenged the skilled artisan at the time of Applicant's invention, as well as on the references' publication date. Whether or not the references qualify as prior art is irrelevant. Regarding Applicants' second point, it is also irrelevant that the references do not specifically relate to HCV antigens. The references teach that modifying the cysteine references of a polypeptide affects antigenicity. There is no reason why this principle would apply to one species of virus, but not another. All viruses comprise proteins that are arranged as a series of amino acids joined peptide bonds.

Thus, whether or not the peptide is from a specific source does not affect how it will respond to cysteine modifications.

Applicant notes that the Examiner failed to rebut the declaration evidence. This argument is not persuasive because the declaration was irrelevant to the enablement rejection. That is, the claims were rejected because the specification did not enable modifying cysteine residues by, *inter alia*, deletion, addition or substitution. The declaration however provided evidence that covalent modification with iodoacetate improved NS3 specificity. This was consistent with the enablement rejection which agreed that the claims were enabled for iodoacetate modification (see p. 3, item (i)). Because the Office action was in agreement with the declaration, there were no assertions that needed to be addressed in the declaration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

Undue experimentation is based on an analysis of the following factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working

examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Here, the specification does not enable the breadth of the claims. The claims are drawn to an immunoassay for detecting HCV antibody comprising contacting a sample with a NS3 polypeptide wherein at least one cysteine of the NS3 polypeptide has been modified. Thus, the claims provide that any combination of the polypeptide's cysteine residues may be modified by deletion, substitution or insertion. These modifications however would have an unpredictable effect on antigenicity. For example, replacing a cysteine with a large heterologous polypeptide would certainly affect the polypeptide's specificity for NS3 antibody. Modifying cysteine residues by point mutation would also have an unpredictable effect as research shows that minor cysteine alterations in antigenic viral proteins can alter specificity. Mutations in the cysteine residues of hepatitis B virus (HBV) surface antigen strongly reduces antibody specificity. (Virol. (1995) 211, 535-543). This is also the case with HBe antigen which shows greatly reduced antigenicity when cysteine is mutated at position 61 (J. Virol. (March 1993) 67, 3, 1315-1321). Modifying any one of the first six cysteines of glycoprotein D causes a complete loss of herpes simplex antibody binding. (J. Virol. (November 1990) 64, 11, 5542-5552). Because the effects of modifying cysteine residues are unpredictable, one skilled in the art would have to turn to the specification in order to improve the specifity of NS3 by cysteine modification. In this regard, the specification provides adequate direction and working examples for (i) NS3 polypeptides modified by covalent attachment of iodoacetate, and (ii) the D26 antigen. However, the modifications that fall outside of this range are not enabled due to the unpredictability noted above. The specification does not point out the specific cysteine changes that improve antigenicity. While the specification indicates that cysteines are preferentially replaced with serine, it does not indicate the specific cysteine residues that can be modified. Thus, one skilled in the art would have to invest in extensive experimentation using site-directed mutagenesis in order to discover which of the invention's NS3 cysteine residues improve antigen

function. Based on this lack of direction and the unpredictable effects cysteine modification, one skilled in the art would have to invest undue experimentation in order to make and use the claimed invention.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy M. Brown whose telephone number is (571) 272-0773. The examiner can normally be reached on Monday - Friday, 8am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Timothy M. Brown
Examiner
Art Unit 1648

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James C. Housel 1/23/06
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